UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/852,157	05/10/2001	Douwe Molenaar	P 278405 990012 BT-CIP	3863

909 7590 04/05/2004

PILLSBURY WINTHROP, LLP
P.O. BOX 10500
MCLEAN, VA 22102

EXAMINER	
RAMIREZ, DELIA M	

ART UNIT	PAPER NUMBER
1652	

DATE MAILED: 04/05/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/852,157	MOLENAAR ET AL.	
	Examiner	Art Unit	
	Delia M. Ramirez	1652	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *09 January 2004*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *16-23* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *16-23* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☒ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Status of the Application

Claims 16-23 are pending.

Applicant's cancellation of claims 1-15, addition of claims 16-23, submission of a declaration regarding a biological deposit, and submission of foreign priority documents in a communication filed on 1/9/2004 are acknowledged.

Rejections and/or objections not reiterated from previous office actions are hereby withdrawn.

Terminal Disclaimer

1. Applicants assert in the response filed on 1/9/2004 (page 11) that a terminal disclaimer was filed. It is noted that no terminal disclaimer could be found in the case and no fees have been charged in regard to a terminal disclaimer according to PTO records.

Claim Rejections - 35 USC § 112, Second Paragraph

2. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

3. Claims 18, 21 and 23 rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

4. Claim 18 is indefinite in the recitation of "the process according to claim 16, wherein said plasmid vector..." as there is no antecedent basis for the plasmid vector. For examination purposes, it will be assumed that the term reads "the process according to claim 17". Correction is required.

5. Claim 21 is indefinite in the recitation of "the process according to claim 19, wherein said plasmid vector..." as there is no antecedent basis for the plasmid vector. For examination purposes, it will be assumed that the term reads "the process according to claim 20". Correction is required.

6. Claim 23 is indefinite in the recitation of "gene encoding for S-(2-aminoethyl)-cysteine resistance" as it is unclear how a gene can encode resistance. For examination purposes, it will be assumed that the term reads "gene encoding an S-(2-aminoethyl)-cysteine resistance protein". Correction is required.

Claim Rejections - 35 USC § 112, First Paragraph

7. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

8. Claims 16, 19, 22 and 23 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

9. This rejection, which has been applied to now cancelled claims 1-15 in Paper No. 5, mailed on 9/9/2003, is now applied to newly added claims 16, 19, 22 and 23 for the reasons of record and those set forth below.

10. Applicants argue that the instant rejection should not be applied to newly added claims 16-23 particularly in view of the fact that the claims are directed to a fermentation process to produce specific amino acids as described in page 7, with a specific mqo gene (from C. glutamicum strain ATCC 13032) and specific bacterial strains (Corynebacterium and

Brevibacterium). Furthermore, Applicants submit that the specification teaches he overexpression of the dapA gene and the gene encoding S-(2-aminoethyl)-cysteine resistance.

11. Applicant's arguments have been fully considered but are not deemed persuasive to avoid the rejection as it applies to newly added claims 16, 19, 22 and 23. The instant claims are drawn to a fermentation process for the preparation of specific amino acids using bacteria wherein (1) the mqo gene from C. glutamicum strain ATCC 13032 is overexpressed, or (2) a C. glutamicum dapA gene, a genus of genes encoding S-(2-aminoethyl)-cysteine resistance proteins from any source, and the mqo gene from C. glutamicum strain ATCC 13032 are overexpressed. The specification (page 5, first paragraph) discloses that overexpression encompasses (1) increasing the copy number of the gene, (2) mutating the promoter/regulatory region of a gene, or (3) lengthening the life of the corresponding mRNA. While overexpression by increasing the copy number of the desired gene using a vector is well known in the art, the specification provides no information as to (1) which mutations in the promoter/regulatory region of the recited genes can be made to obtain overexpression, or (2) methods to lengthening the life of the corresponding mRNA. Furthermore, as indicated in Paper No. 5, the genus of genes encoding S-(2-aminoethyl)-cysteine resistance proteins has not been adequately described as their structures have not been disclosed and the specification is silent in regard to the structural elements which are characteristic of any gene encoding an S-(2-aminoethyl)-cysteine resistance protein.

The genus of genes required to practice the claimed process is potentially a large and structurally variable genus. While a sufficient written description of a genus of nucleic acids may be achieved by a recitation of a representative number of nucleic acids defined by their nucleotide sequence or a recitation of structural features common to members of the genus, which features constitute a substantial portion of the genus., in the instant case, there is no structural feature which is representative of all the members of the genus of genes recited in the claim. In addition, it is reiterated herein that while one could argue that the genus of genes recited in the claims is

adequately described since they can be isolated by sequence comparison with other known genes, the state of the art teaches that even high structural homology may not result in functional homology. Therefore, in view of the information provided by the specification, one cannot reasonably conclude that the claimed method is adequately described.

12. Claims 16-23 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

13. This rejection, which has been applied to now cancelled claims 1-15 in Paper No. 5, mailed on 9/9/2003, is now applied to newly added claims 16-23 for the reasons of record.

14. Applicants argue that the specification provides clear operability and guidance through the working examples. Specifically, Applicants refer to Tables 1 and 2 and submit that the results unequivocally demonstrate that overexpression of mqo increases L- amino acid production. Furthermore, Applicants indicate that nearly every genetic and biological component is the same between DSM5715::pJC1 and DSM5715::pRM17 except for the fact that DSM5715::pRM17 contains the full length mqo gene. According to Applicants, it is irrelevant if copending Application No. 10/118325 discloses opposing teachings in view of what is disclosed in the instant application, and submit that through their declarations, they have attested that their results demonstrate an increase in L-amino acid levels due to overexpression of the mqo gene.

15. Applicant's arguments have been fully considered but are not deemed persuasive to avoid the rejection of newly added claims 16-23. The Examiner acknowledges the teachings of the specification, the working examples provided and the results of Table 1 and 2. However, the Examiner disagrees with Applicant's contention that the opposing teachings of copending Application No. 10/118325 are irrelevant to the examination of the instant application. The

method of application No. 10/118325 uses the same mqo gene (from C. glutamicum strain ATCC 13032), as described in Example 1 of application No. 10/118325, and the same C. glutamicum strain in the fermentation process (C. glutamicum DSM5715), as described in Example 3 of application No. 10/118325. Thus, based on the information provided in application No. 10/118325, nearly every genetic and biological component is the same between DSM5715 and DSM5715::pXK99Emobmqo except for the fact that DSM5715::pXK99Emobmqo contains a fragment of the C. glutamicum mqo gene (incomplete gene). Absence experimental evidence explaining the contradicting results in the instant application and copending application 10/118325, it is unclear as to how one of skill in the art can reasonably conclude that the claimed invention is enabled by the specification.

16. Even if Applicants can overcome the enablement rejection applied above in regard to the operability of the claimed method, the following rejection would also apply. Claims 16-23 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method for producing L-lysine or L-threonine in Corynebacterium or Brevibacterium which has been transformed with a plasmid comprising the C. glutamicum strain ATCC 13032 malate:quinone oxidoreductase (mqo) gene such that said gene is overexpressed and the intracellular activity of the C. glutamicum mqo is increased, and wherein said Corynebacterium or Brevibacterium is further transformed with a plasmid comprising the C. glutamicum dapA gene and/or the gene encoding the S-(2-aminoethyl)-cysteine resistance protein disclosed in EP-A 0 088 166 such that said genes are overexpressed and the intracellular activity of the gene products is increased, does not reasonably provide enablement for a (1) method as described above for production of L-aspartic acid, L-asparagine, L-homoserine, L-isoleucine, or L-methionine, (2) method as describe above for production of L-lysine or L-threonine by mutating the promoter/regulatory region of the C. glutamicum strain ATCC 13032 mqo and/or the C.

glutamicum dapA genes, or lengthening the life of the corresponding mRNAs, or (3) a method as described above wherein any gene encoding an S-(2-aminoethyl)-cysteine resistance protein is overexpressed as defined in the specification. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention commensurate in scope with these claims.

17. This rejection, which has been applied to now cancelled claims 1-15 in Paper No. 5, mailed on 9/9/2003, is now applied to newly added claims 16-23 for the reasons of record.

18. Applicants argue that the new claims are directed to subject matter which is enabled by the specification. Specifically, Applicants indicate that there is enablement for transforming other Corynebacteria and Brevibacteria with the C. glutamicum strain ATCC 13032 mqo gene to overproduce not only L-lysine and L-threonine but also L-aspartic acid, L-asparagine, L-homoserine, L-isoleucine, and L-methionine. Therefore, Applicants submit that a rejection of new claims 16-23 on the same grounds would be improper.

19. Applicant's arguments have been fully considered but are not deemed persuasive to avoid the rejection as it relates to claims 16-23. While it is agreed that the instant claims are limited in regard to the bacteria to be fermented, the mqo gene used, and the amino acids produced, claims 16, 19, 22-23 are still drawn to a fermentation process which requires overexpression of the recited genes by (1) mutating the promoter/regulatory region of a gene, or (2) lengthening the life of the corresponding mRNA. See discussion above regarding the definition of overexpression provided in the specification. While overexpression by increasing the copy number of the desired gene using a vector is well known in the art, the specification provides no information as to (1) which mutations in the promoter/regulatory region of the recited genes can be made to obtain overexpression, or (2) methods to lengthening the life of the corresponding mRNA. Furthermore, claims 16-21 are directed to a fermentation process for producing L-aspartic acid, L-asparagine, L-homoserine, L-isoleucine, or L-methionine, however the specification provides

no evidence to show that these amino acids can be prepared by the claimed method nor does it provide any reasoning as to why one of skill in the art would reasonably conclude that these amino acids can be prepared by the claimed method. While claim 23 is directed to a fermentation process for the preparation of L-lysine, the claim also requires the overexpression of genes for which no structure has been disclosed, i.e. genes encoding an S-(2-aminoethyl)-cysteine resistance protein. In addition, the specification is silent as to the structural elements which are characteristic of genes encoding an S-(2-aminoethyl)-cysteine resistance protein and the state of the art, as previously discussed in Paper No. 5, teaches the unpredictability of isolating functional homologs based solely on structural homology. Thus, for the reasons set forth above, one cannot reasonably conclude that the full scope of the claimed invention is enabled by the specification.

Double Patenting

20. Claims 1-2, 4-5, 11 and 15 were provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over (1) claim 15 of copending Application No. 09/804073 (common assignee Degussa AG), (2) claim 14 of copending Application No. 09/770688 (common assignee Degussa AG), and (3) claims 16-17 of copending Application No. 09/733386 (common inventor Bettina Mockel).

21. Applicants submit that applications 09/804073, 09/770688, and 09/733386 were abandoned and the rejections should be withdrawn. Cancellation of claims 1-2, 4-5, 11 and 15 render these rejections moot as applied to claims 1-2, 4-5, 11 and 15. In view of the fact that applications No. 09/804073, 09/770688, and 09/733386 are now abandoned, these rejections are not applicable to any of newly added claims 16-23.

22. Claims 1-3, 5, and 11 were provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claim 24 of copending Application No. 09/796431 (common assignee Degussa AG).

23. Cancellation of claims 1-3, 5 and 11 render these rejections moot as applied to claims 1-3, 5 and 11. In view of the fact that newly added claims 16-23 are directed to a fermentation process for the production of L-aspartic acid, L-asparagine, L-homoserine, L-threonine, L-isoleucine, L-lysine, or L-methionine, and claim 24 of copending Application No. 09/796431 is directed to a fermentation process for the production of L-glutamic acid, this rejection is not applicable to any of newly added claims 16-23.

24. Claims 16-17, 19-20, and 22-23 are provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claim 10 of copending Application No. 10/178219 (common inventor Bettina Mockel).

25. Claims 16-17, 19-20, and 22-23 are provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claim 14 of copending Application No. 10/375355 (common assignee Degussa AG).

26. Claims 16-17, 19-20, and 22-23 are provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claim 18 of copending Application No. 09/938540 (common inventor Bettina Mockel).

27. These rejections were previously applied to now canceled claims 1-2, 4-5, 11 and 15. Applicants have indicated that a terminal disclaimer obviating these rejections was filed concurrently with the response filed on 1/9/2004. As indicated above, no terminal disclaimer could be found. Thus, the instant rejections are now applied to newly added claims 16-17, 19-20, and 22-23 for the reasons of record and for the reasons set forth below. The fermentation processes for the production of L-lysine of claim 10 of copending Application No. 10/178219,

claim 14 of copending Application No. 10/375355, and claim 18 of copending Application No. 09/938540 are all disclosed in the corresponding applications as being practiced with the mqo gene from C. glutamicum strain ATCC 13032. Copending applications No. 10/178219, 10/375355, and 09/938540 disclosed practicing the claimed fermentation processes with the mqo gene from C. glutamicum strain ATCC 13032 as a preferred embodiment. See references to the mqo gene disclosed by Molenaar et al. (Eur. J. Biochem. 254:395-403, 1998) in paragraphs 34, 89, and 93 of the corresponding US publication of applications 10/178219, 10/375355, and 09/938540, respectively. The mqo gene disclosed by Molenaar et al. is that of C. glutamicum strain ATCC 13032. Therefore, claim 10 of copending Application No. 10/178219, claim 14 of copending Application No. 10/375355, and claim 18 of copending Application No. 09/938540 would anticipate newly added claims 16-17, 19-20 and 22-23 as written.

Conclusion

28. No claim is in condition for allowance.

29. Applicant's amendment canceling claims 1-16 and adding new claims 16-23 necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event,

however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

30. Certain papers related to this application may be submitted to Art Unit 1652 by facsimile transmission. The FAX number is (703) 872-9306. The faxing of such papers must conform with the notices published in the Official Gazette, 1156 OG 61 (November 16, 1993) and 1157 OG 94 (December 28, 1993) (see 37 CFR 1.6(d)). NOTE: If Applicant submits a paper by FAX, the original copy should be retained by Applicant or Applicant's representative. NO DUPLICATE COPIES SHOULD BE SUBMITTED, so as to avoid the processing of duplicate papers in the Office.

31. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Delia M. Ramirez whose telephone number is (571) 272-0938. The examiner can normally be reached on Monday-Friday from 8:30 AM to 5:00 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Dr. Ponnathapura Achutamurthy can be reached on (571) 272-0928. Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (703) 308-1234.

Delia M. Ramirez, Ph.D.
Patent Examiner
Art Unit 1652

DR
April 1, 2004

REBECCA E. PROUTY
PRIMARY EXAMINER
GROUP ~~1800~~ 1600